Clinical Edit Proposal

Drug/Drug Class: **Suboxone® (Buprenorphine/Naloxone)/ Partial opioid agonist/opioid antagonist**

Prepared for: Missouri Medicaid
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☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:

The purpose of this monograph is to provide an extensive review of new therapy to determine whether the reviewed drug should be made available on an open access basis, apply clinical edit or require prior authorization for use.

Dosage Forms & Manufacturer:

- Sublingual hexagonal orange tablet containing either
  - 2 mg buprenorphine with 0.5 mg naloxone, or
  - 8 mg buprenorphine with 2 mg naloxone
- Also available as 2 mg and 8 mg sublingual tablets containing only buprenorphine (Subutex®)
- Reckitt Benckiser Pharmaceuticals, Inc.: Richmond, VA

Summary of Findings:

Buprenorphine/naloxone (Suboxone®) and buprenorphine (Subutex®) are sublingual tablets recently approved by the FDA for the treatment of opioid dependence. When compared to methadone, potential advantages of buprenorphine treatment (e.g., fewer withdrawal symptoms, less potential for abuse, long duration of action) must be considered in the context of its somewhat inferior efficacy profile and greater acquisition cost. Given its slightly inferior efficacy compared to methadone, the significant cost impact, and the uncertainty surrounding most appropriate candidates for treatment, it is recommended that buprenorphine/naloxone (Suboxone®) be subject to a clinical edit in order to optimize its effectiveness.

Status Recommendation:

☐ Prior Authorization (PA) Required ☐ Open Access
☒ Clinical Edit

Type of PA Criteria:

☐ Increased Risk of ADE ☐ Non-Preferred Agent
☒ Appropriate Indications ☐ PA Not Required

Purpose

The purpose of this monograph is to provide an extensive review of new therapy to determine whether the reviewed drug should be made available on an open access basis, apply clinical edit or require prior authorization for use. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement o f qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

Buprenorphine/naloxone (Suboxone®) and buprenorphine alone (Subutex®) are sublingual tablets recently approved by the FDA for the treatment of opioid dependence. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor while naloxone is an antagonist at the mu-opioid receptor. Other opioid agonists indicated for the treatment of opioid dependence are methadone and levomethadyl acetate (Orlaam®). These Schedule II agents are currently available only through federally regulated treatment clinics. Buprenorphine/naloxone and buprenorphine alone, as Schedule III agents, are the first opioid agents available for the treatment of opiate dependence that can be prescribed in an office setting, under the Drug Addiction Treatment Act (DATA) of 2000.[1] DATA allows qualified physicians to prescribe Schedule III, IV, and V medications that are approved for the treatment of opioid dependence.[1] Physicians must be certified in addiction medicine or addiction psychiatry, have completed at least 8 hours of authorized training, or have been an investigator in a clinical trial leading to the approval of Suboxone®/Subutex®.[2]

Dosage Form(s)[3]

- Suboxone® is a sublingual hexagonal orange tablet containing either 2 mg buprenorphine with 0.5 mg naloxone, or 8 mg buprenorphine with 2 mg naloxone.
- Subutex® is an oval white tablet containing either 2 mg or 8 mg or buprenorphine.

Manufacturer

Reckitt Benckiser Pharmaceuticals, Inc.: Richmond, VA 23235

Indication(s)[3]

Suboxone® and Subutex® are indicated for the treatment of opioid dependence.

Clinical Efficacy (mechanism of action/pharmacology, comparative efficacy)

Mechanism of Action/Pharmacology

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is an antagonist at the mu-opioid receptor.

In non-dependent subjects, buprenorphine produces typical opioid agonist effects such as analgesia, sedation, nausea and dizziness, but these are limited by a ceiling effect in most patients with sublingual doses of 24 to 32 mg.[3] In patients physically dependent on mu-receptor agonists such as morphine or heroin, buprenorphine usually prevents symptoms of withdrawal, but in high doses it can act a as an antagonists and precipitate withdrawal symptoms.[4] In non-dependent subjects, there were no statistically significant differences between buprenorphine 12 mg sublingual and placebo with respect to blood pressure, heart rate, respiratory rate, O_2 saturation or skin temperature across time.[3]

Naloxone, in the Suboxone® formulation, had no clinically significant effect when administered by the sublingual route, although blood levels of the drug were measurable. When administered parenterally, naloxone reverses the effects of most opiates; therefore, its presence in Suboxone® tablets is intended to discourage intravenous abuse of buprenorphine by opioid-dependent patients.[3]

Comparative Efficacy

Two comprehensive systematic reviews recently have been published that analyze the efficacy and safety of buprenorphine/naloxone in treating withdrawal from opioid dependence and in short-term maintenance for opioid dependence.[5,6] These reviews encompass most of the published and unpublished randomized clinical trials of buprenorphine for these indications and their findings are summarized below. It should be noted that studies analyzed used either buprenorphine sublingual tablet formulations, with and without naloxone, or sublingual administration of a more bioavailable ethanolic solution of buprenorphine.

One systematic review assessed the efficacy of short-term buprenorphine to manage the acute phase of opioid withdrawal.[5] This analysis included 6 studies (5 randomized controlled trials [RCTs] and 1 controlled prospective study) involving 357 patients. Four studies compared buprenorphine with clonidine. All found withdrawal to be less severe in the buprenorphine treatment group. In 3 of these studies, all participants were withdrawing from heroin, while participants in one study were withdrawing from methadone (10 mg/day). The reviewers concluded that buprenorphine has potential as a medication to ameliorate the signs and symptoms of withdrawal from heroin, and possibly methadone, but that further investigation is needed.

Mattick et al.[6], analyzed 13 randomized clinical trials (all but one were double-blind) to evaluate the effects of buprenorphine maintenance against placebo or methadone or levomethadyl acetate maintenance for opioid dependence. In this meta-analysis, buprenorphine given in flexible doses appeared slightly, but statistically significantly, less effective than methadone in retaining patients in treatment (RR=0.82; 95% CI:0.69-0.96). Low dose buprenorphine (2 to 4 mg) was not superior to low dose methadone (20 to 35 mg) High dose buprenorphine (6 to 12 mg) did not retain more patients than low dose methadone, but may suppress heroin use better. There was no advantage for high dose buprenorphine over high dose methadone (60 to 80 mg) in retention (RR=0.79; 95%

CI: 0.62-1.01), and high dose buprenorphine was inferior in suppression of heroin use. Buprenorphine was superior to placebo in retention of patients in treatment at low doses (RR=1.24; 95% CI: 10.6-1.45), high doses (RR=1.21;95% CI: 10.2-2.44), and very high doses (RR=1.52;95% CI:1.23-1.88). Buprenorphine high and very high doses also suppressed heroin use significantly more than placebo. The reviewers concluded that buprenorphine is an effective intervention for use in the maintenance treatment of heroin dependence, but it is not more effective than methadone at adequate dosages.[6]

Several potential explanations for the slightly poorer retention in buprenorphine treatment vs. methadone have been proposed:[6]

- Induction onto buprenorphine was carried out too slowly.
- Partial agonist vs. full opioid effect is less satisfying to patients.
- Patients in the initial stages of dosing who have recently ingested heroin suffer a mild withdrawal syndrome by virtue of buprenorphine (partial agonist) displacing heroin (a full agonist) from opioid receptors.
- Buprenorphine is easier to withdraw from, so patients are at more liberty to leave treatment without the severe withdrawal syndrome that can accompany methadone withdrawal.

The reviewers also point out that some doses used in the high dose methadone conditions in the analysis are rarely used in day-to-day clinical practice, where the average range is 50 to 60 mg. At this level, there does not appear to be any reliable difference in heroin use between methadone and buprenorphine, overall.[6]

Contraindications[3]

Buprenorphine/naloxone should not be given to patients with hypersensitivity to either agent.

Warnings[3]

Respiratory Depression

Serious respiratory depression has been associated with buprenorphine, especially by the intravenous route. Deaths have been reported in association with concomitant administration of other depressants such as alcohol or other opioids, or when addicts have intravenously misused buprenorphine, usually with concomitant benzodiazepines. Naloxone may not be effective in reversing buprenorphine-induced respiratory depression because of the latter's prolonged occupancy of the mu receptor.

Suboxone® and Subutex® should be used with caution in patients with compromised respiratory function.

Dependence

Chronic administration of buprenorphine produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset due to prolonged occupancy of the mu receptor.[3,4]

Hepatitis/hepatic events

Cases of cytolytic hepatitis and hepatitis with jaundice have occurred in patients receiving buprenorphine. Other hepatic abnormalities have been observed, ranging from liver function test (LFT) elevations to hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic

encephalopathy. In many cases, the presence of pre-existing LFT abnormalities, infection with hepatitis B or C virus, concomitant use of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. Nevertheless, it is recommended that LFTs be checked prior to start of therapy, and then periodically thereafter.

Opioid withdrawal effects

Because it contains naloxone, Suboxone® is highly likely to produce marked and intense withdrawal symptoms if misused parenterally by individuals dependent on opioid agonists such as heroin, morphine, or methadone. Sublingually, Suboxone® may cause opioid withdrawal symptoms in such persons if administered before the agonist effects of the opioid have subsided.

Other precautions

In general, Suboxone® and Subutex® should be administered with caution in elderly or debilitated patients and those with severe impairment of hepatic, pulmonary, or renal function; myxedema or hypothyroidism, adrenal cortical insufficiency; CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

The dose of buprenorphine/naloxone should be adjusted in patients with moderate or severe hepatic impairment, and the patient monitored for symptoms of precipitated opiate withdrawal.

Neonatal withdrawal has been reported in the infants of women treated with buprenorphine during pregnancy. The time to onset of neonatal withdrawal symptoms ranged from Day 1 to Day 8 of life with most occurring on Day 1.

Adverse Effects[3]

The most common adverse effects associated with buprenorphine/naloxone include headache, abdominal pain, nausea, sweating, insomnia and constipation. While some e are typical opioid effects (e.g., constipation, nausea), others represent withdrawal symptoms that are possible at high doses (e.g., sweating, abdominal pain, insomnia, and flu-like symptoms).

Drug Interactions[3]

Buprenorphine is metabolized by CYP3A4. Because inhibitors of CYP3A4 may increase plasma concentrations of buprenorphine, patients already on such agents (e.g., azole antifungals, macrolide antibiotics, and HIV protease inhibitors) should have their dose of Suboxone® or Subutex® adjusted.

Increased CNS depression is possible when buprenorphine is administered in the presence of other CNS depressants, including alcohol. Reduction of the dose of one or both agents should be considered.

There may be an interaction between buprenorphine and benzodiazepines. There have been reports of coma and death associated with the misuse of buprenorphine (i.e., self-injection of crushed buprenorphine tablets) with benzodiazepines. Patients should be warned of the potential danger of the intravenous self-administration of benzodiazepines while under treatment with Suboxone® or Subutex®.

Dosage and Administration[3]

Suboxone® and Subutex® are administered sublingually as a single daily dose in the range of 12 to 16 mg/day. Subutex® is preferred for induction because it contains no naloxone. While the amount of naloxone absorbed sublingually (from Suboxone®) is very small, it could theoretically precipitate withdrawal in some patients. Suboxone® is preferred for maintenance treatment that includes unsupervised administration. Naloxone has been added to this formulation to deter patients from crushing and injecting the tablets.

The tablets should be placed under the tongue until they are dissolved. For doses requiring the use of more than two tablets at a time, patients can either take all of the tablets at once or place two tablets at a time under the tongue. Patients should not swallow the tablets since this decreases bioavailability of the drug. Patients should be advised to take the tablets the same way throughout therapy for consistency.

Induction: In a clinical study, patients received 8 mg of Subutex® on Day 1 and 16 mg on Day 2. From Day 3 onward, patients received Suboxone® in the same dose as at Day 2. To avoid precipitating withdrawal, the drug should be administered at least 4 hours after the patient's last heroin dose (or at least 24 hours after the last methadone dose) or, preferably, when early sings of opioid withdrawal appear. To avoid patient drop-out, an adequate maintenance dose should be achieved as quickly as possible.

Maintenance: The recommended target dose of Suboxone® is 16 mg/day, but 12 mg/day may be effective in some patients. The dose should be adjusted in increments/decrements of 2 mg or 4 mg to a level that holds the patient in treatment and suppresses opioid withdrawal effects. This is likely to be in the range of 4 mg to 24 mg/day.

Although not FDA-approved for dosing less frequent than once daily, clinical trials have demonstrated the comparable efficacy of a three times weekly vs. a once daily buprenorphine regimen (each consisting of the same total weekly dose).[7]

Cost Comparison

Table 1. Costs of opiate therapies for the treatment of opioid dependence

Drug	Typical dose regimen	Cost per 4 weeks of therapy (AWP)
Buprenorphine/naloxone (Suboxone)	16 mg/day	$288
Buprenorphine (Subutex)	16mg/day	$350
Methadone	50-60 mg/day	$25 - $34
Levomethadyl acetate (Orlaam) [2]	75-100 mg 3x/week	$43 - $58

*Average Wholesale Price: Facts and Comparisons (Medi-Span), St Louis, MO; May 2003.

Conclusion

Buprenorphine/naloxone (Suboxone®) and buprenorphine alone (Subutex®) are sublingual tablets recently approved by the FDA for the treatment of opioid dependence. Buprenorphine is a partial

agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor while naloxone is an antagonist at the mu-opioid receptor. As Schedule III drugs, Suboxone® and Subutex® are the first opioid agents available for the treatment of opiate dependence that can be prescribed in an office setting, under the Drug Addiction Treatment Act (DATA) of 2000. Other opioid agonists indicated for the treatment of opioid dependence (methadone and levomethadyl acetate; both Schedule II agents) are currently available only through federally regulated treatment clinics. Of these, methadone is the agent of choice, with levomethadyl being relegated to second-line use, in large part because it is associated with prolonged-QT syndrome and arrhythmias.[8]

The results of two comprehensive systematic reviews show that buprenorphine is an effective treatment for opioid dependence in a maintenance therapy approach, although methadone maintenance treatment at high doses is associated with somewhat higher rates of retention in treatment and better suppression of illicit opioid use.[5,6] As noted above, however, at the 'moderate' methadone dose range of 50 to 60 mg typically used in day-to-day clinical practice, there does not appear to be any reliable difference in heroin use between methadone and buprenorphine, overall.[6]

Because of its pharmacologic differences compared to full opioid agonists, buprenorphine may be associated with fewer withdrawal symptoms and have less potential for abuse, respiratory depression, and overdose compared with methadone and levomethadyl.[9] In addition, its long duration of action may allow for a three times weekly schedule, compared to the daily schedule required for methadone.[7] Another issue to consider are the potential advantages associated with office-based care for opioid dependent patients that are possible with buprenorphine but not with methadone or levomethadyl: increased patient access to treatment, enhanced privacy for the patient, and limitation of the patients' contact with other drug-abusing patients.[8]

These significant potential advantages of buprenorphine treatment must be considered in the context of its somewhat inferior efficacy profile compared to high dose methadone and its significantly greater acquisition cost. Furthermore, an important unanswered question about office-based treatment of opioid dependence is patient selection.[9] Several programs that involved transfer of patients from a methadone treatment program to office based maintenance therapy have established criteria to identify potentially successful patients (Table 2).[8,9] However, for patients initiating treatment through a physician's office, criteria to identify appropriate candidates are less clear.

Table 2. Characteristics of appropriate candidates for office-based care of opioid dependence[8]

- Enrollment in maintenance program for 1 - 5 years*
- Clinical stability as evidenced by 1 year of illicit-drug-negative urine specimens*
- No evidence of dependence on cocaine, alcohol, or other drugs, except nicotine
- No untreated psychiatric conditions
- Presence of a stable source of financial support
- Presence of a stable source of coverage for medication and office visits
- Absence of involvement in illegal activities
- Compliance with treatment regimen
- No history of multiple relapses after treatment

*Refers specifically to transfer from an opioid treatment program to office-based care vs. initiating treatment through a physician's office

Recommendation(s)

Given its slightly inferior efficacy compared to methadone, the significant cost impact, and the uncertainty surrounding most appropriate candidates for treatment, it is recommended that buprenorphine (either alone as Subutex® or with naloxone as Suboxone®) be subject to a clinical edit in order to optimize its effectiveness.

Approval Criteria

- Diagnosis equals Opoid Drug Dependence in last two year
- Physician has Substance Abuse and Mental Health Services (SAMSA) Waiver
- Patient must be under the care of one primary physician

Denial Criteria

- Lack of approval criteria

References

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